Stereoselective, Dual-Mode Ruthenium-Catalyzed
Ring Expansion of Alkynylcyclopropanols
Barry M. Trost, Jia Xie, and Nuno Maulide

stress and catechol are not compatible with other oxidation states of copper, such as Cu(I) or Cu(II) complexes, which are known to be involved in the oxidation of catechol to dopamine. The use of copper(III) complexes provides a unique opportunity to study the oxidation of catechol to dopamine under conditions that are not accessible with other redox states. This work also underscores the importance of considering the redox properties of metal complexes in the design of new molecular probes for dopamine. The results presented here highlight the potential of copper(III) complexes as a tool for studying dopamine metabolism and its relevance to neuropsychiatric disorders.
The fascinating chemistry of small-ring compounds stems almost invariably from the unique reactivity modes allowed by the intrinsic ring strain. In particular, ring-expansion reactions have been abundantly used in organic synthesis to efficiently and expeditiously fashion functionalized molecules, and the appearance of various transition metal-catalyzed ring expansion processes has only enriched this landscape.

There is a considerable body of work on the transition metal catalyzed ring expansion of vinyl and allenyl cycloalkanols, providing useful tools for construction of various cyclic ketones. This contrasts with the scarcity of reports of transition metal promoted skeletal rearrangements of alkynylcycloalkanols.

Our recent interest in tapping the potential of alkynes as selective mediators in metal-catalyzed bond-forming reactions led us to speculate whether Ru catalysis would provide an interesting addition to the current arsenal of ring-expansion processes. The remote analogy between the isomerization of a propargyl alcohol to an unsaturated carboxyl (termed the redox isomerization reaction) and the skeletal rearrangement of a tertiary cyclopropyl carbinol further spurred our interest. We report that Ru catalysis is unique in the activation of alkynyl cyclopropanols as it mediates a highly selective, dual ring expansion to either four- or five-membered cyclic ketones.

Our initial forays were successful. Treatment of the TMS-substituted alkynylcyclopropanol with catalytic amounts of Ru complex in essentially quantitative yield. Interestingly, the least stable (Z)-isomer was formed with nearly 6:1 stereoselectivity (Table 1, entry 1). Our curiosity piqued, the little precedent found for the expansion of alkynyl cyclopropanols prompted us to examine further this class of substrates (results in Table 1).

The trend for the preferential formation of (Z)-silylalkylidene cyclobutanones upon exposure to our conditions appears to be quite general. As the steric bulk of the silyl substituent increases, so does the Z/E ratio. The corollary of this premise is that the highly congested TIPS-substituted alkynylcyclopropanol smoothly triggered ring expansion to alkylidene cyclobutanones with nearly 6:1 stereoselectivity (Table 1, entry 1).

Realizing that the electronic properties of silyl moieties might be playing a prominent role in this outcome, we then examined electron-withdrawing substituents (results in Table 2).

In contrast to the silyl-substituted substrates, in this case the conversion was slower, which could be ascribed to the lower electron density at the alkyne (vide infra). Nonetheless, good yields of alkylidene cyclobutanones were obtained and this regardless of the nature of the ester group (aliphatic, benzylic or nitroaromatic) also does not affect the outcome of the reaction. Importantly, and in analogy with the case of silyl-substituted alkynylcyclopropanols (cf. Table 1), a single isomer was obtained in all cases, which was assigned the (Z)-configuration. Note that the stereochemical outcome for these reactions is the precise opposite of what was reported using Au catalysis, suggesting that different mechanistic pathways may be operative in each case.

Observing the ability of our catalytic system to efficiently convert silyl- and acceptor-substituted alkynylcyclopropanols to stereoselectively.
fined alkylidene cyclobutanones, we probed the stereoselectivity of the analogous process employing electron-“neutral” alkyl substituents at the alkyne.

When we exposed the hexyl-substituted alkynlycyclopropanol 10a to our reaction conditions (eq 1), the anticipated cyclobutanone 11a did not form but rather the unexpected β-substituted cyclopentenone 12a.

![Scheme 2. Mechanistic Proposal for the Dual Ring Expansions](image)

Ru to selectively mediate either of the two pathways depending on the electronic properties of the substrate bears testament to the versatile nature of this metal in catalysis. In particular, the ability to access functionalized β-substituted cyclopentenones through a direct two-carbon homologation is appealing. Moreover, the exclusive obtention of the (Z)-alkylidene cyclobutanone isomers through the cyclopropanol/cyclopentenone expansion manifold is unprecedented and serves to further distinguish Ru from other, alkynophilic transition metals.

Acknowledgment. We thank the NSF and NIH (NIH-13598) for generous support of our programs. N.M. is grateful to the Fundação para a Ciência e Tecnologia (FCT) for a postdoctoral fellowship. We thank Johnson-Matthey for a generous gift of Ru salts.

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References


Ru-Catalyzed Ring Expansion of Alkyl-Substituted Alkynlycyclopropanols to Cyclopentenones

In summary, we have developed a novel Ru-catalyzed ring expansion of alkynlycyclopropanols. This atom-economic reaction appears to proceed by two different pathways. The unique ability of

Table 3. Ru-Catalyzed Ring Expansion of Alkyl-Substituted Alkynlycyclopropanols to Cyclopentenones

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* Yields refer to pure, isolated products.